

**What is claimed is:**

1. A method of detecting a polymorphic site in a sample to determine alpha-2B-adrenergic receptor function, comprising:
  - a. obtaining the sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide; and
  - b. detecting in the sample a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof.
- 5 2. A method according to claim 1, wherein the polymorphic site comprises SEQ ID NO: 3 or 4 or complement thereof.
3. A method according to claim 2, wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1.
4. A method according to claim 2, wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2.
- 10 5. A method according to claim 2, wherein the complement of the polymorphic site comprises SEQ ID NO: 5 or 6.
6. A method of genotyping an alpha-2B-adrenergic receptor gene comprising:
  - a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide; and
  - b. detecting in the sample a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof.

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7. A method according to claim 6, wherein the genotyping is performed on two copies of the alpha-2B-adrenergic receptor gene.
8. A method according to claim 6, wherein the polymorphic site comprises SEQ ID NO: 3 or 4 or complement thereof.
9. A method according to claim 6, wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1.
10. A method according to claim 6, wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2.
11. A method according to claim 6, wherein the complement of the polymorphic site comprises SEQ ID NO: 5 or 6.
12. A method according to claim 6, wherein the detection of the polymorphic site is by dideoxy sequencing, restriction digestion, allele-specific polymerase reaction, single-stranded conformational polymorphism analysis, genetic bit analysis, temperature gradient gel electrophoresis, ligase chain reaction, ligase/polymerase genetic bit analysis, or random amplification DNA.
13. A method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule from a sample comprising performing a primer extension reaction employing an oligonucleotide comprising a nucleotide position 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof.
14. A method according to claim 13, wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50 nucleotides.
15. A method according to claim 13, wherein the primer extension reaction is a single-nucleotide primer extension reaction.
16. A method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule from a sample of an individual, comprising:

a. isolating from the individual the sample having a polynucleotide encoding the alpha-2B adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement thereof;

5 b. incubating the polynucleotide with at least one oligonucleotide, the oligonucleotide having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of the nucleotide present at a polymorphic site of the polynucleotide, wherein the incubation is under conditions sufficient to allow specific hybridization to occur  
10 between complementary nucleic acid molecules;

c. permitting the hybridization to occur; and

d. identifying the polymorphic site to obtain the genotype of the individual, wherein the polymorphic site comprises an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 .

15 17. A method according to claim 16, further comprising amplifying the polymorphic site of the polynucleotide prior to the hybridization.

18. A method according to claim 16, wherein the oligonucleotide is selected from the group consisting of

5'-GCTCATCATCCCTTCTCGCT-3' (SEQ ID NO: 13);

20 5'- AAAGCCCCACCATGGTCGGGT-3' (SEQ ID NO: 14);

5'-CTGATGCCAACGAGCAAC-3' (SEQ ID NO: 15);

5'-AAAAACGCCAATGACCACAG-3' (SEQ ID NO: 16);

5- 'TGTAAAACGACGCCAGT-3' (SEQ ID NO: 17);

5'-CAGGAAACAGCTATGACC-3' (SEQ ID NO: 18);

5'-AGAAGGAGGGTGTGTGGGG-3' (SEQ ID NO: 19);

5'- ACCTATAGCACCCACGCCCT-3'(SEQ ID NO: 20);

5'-GGCCGACGCTCTTGTCTAGCC-3' (SEQ ID NO: 21);

5       5'-CAAGGGGTTCTAACAGATGAG-3' (SEQ ID NO: 22); and complementary sequences thereof.

19. A method according to claim 16, wherein the hybridization is selected from the group consisting of southern blot, dot blot, reverse dot blot, northern blot, and allele-specific oligonucleotide hybridization.

10      20. A method according to claim 16, wherein the oligonucleotide is labeled with a label selected from the group consisting of radiolabel, fluorescent label, bioluminescent label, chemiluminescent label, nucleic acid label, hapten label, and enzyme label.

15      21. A method according to claim 16, wherein the identity of the polymorphic site is determined by dideoxy sequencing, restriction digestion, allele-specific polymerase reaction, single-stranded conformational polymorphism analysis, genetic bit analysis, temperature gradient gel electrophoresis, ligase chain reaction, or ligase/polymerase genetic bit analysis, or random amplification DNA.

22. A method according to claim 16, wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50 nucleotides.

20      23. A method of detecting a polymorphic site in a sample to determine alpha-2B-adrenergic receptor function, comprising:

          a. obtaining the sample having an alpha-2B-adrenergic receptor molecule comprising amino acid SEQ ID NO: 7 or 8 or fragment thereof; and

b. detecting in the sample the polymorphic site at amino acid positions 294 to 309 of SEQ ID NO: 7 or 8.

24. A method according to claim 25, wherein the polymorphic site comprises SEQ ID NO: 9 or 10.

5 25. A method according to claim 25, wherein the polymorphic site is an insertion of 3 glutamic acids at amino acid positions 301 to 303 of SEQ ID NO: 7.

26. A method according to claim 27, wherein the polymorphic site is a deletion of 3 glutamic acids at amino acid positions 301 to 303 of SEQ ID NO: 8.

27. A method of detecting a polymorphic site to determine alpha-2B-adrenergic receptor function, comprising:

a. obtaining a sample having an alpha-2B-adrenergic receptor molecule comprising amino acid SEQ ID NO: 7 or 8 or fragment thereof;

b. contacting the sample with an antibody specifically reactive with the polymorphic site at amino acid positions 294 to 309 of SEQ ID NO: 7 or 8; and

c. detecting in the sample a complex formed between the antibody and amino acid positions 294 to 309 of SEQ ID NO: 7 or 8.

10 28. A method according to claim 27, wherein the polymorphic site is an insertion of 3 glutamic acids at amino acid positions 301 to 303 of SEQ ID NO: 7.

15 29. A method according to claim 27, wherein the polymorphic site is a deletion of 3 glutamic acids at amino acid positions 301 to 303 of SEQ ID NO: 8.

20 30. A method of haplotyping an alpha-2B-adrenergic receptor gene comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide;

b. detecting in the sample a polymorphic site comprising nucleotide positions 5 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof on one copy of the alpha-2B-adrenergic receptor gene; and

c. determining the identity of an additional polymorphic site on the copy of the alpha-2B-adrenergic receptor gene.

31. A method for determining an individual at increased risk for developing a disease associated with an alpha-2B-adrenergic receptor molecule comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide from the individual; and

b. detecting in the sample a polymorphic site comprising nucleotide positions 10 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease, thereby identifying the individual at increased risk for the disease.

32. A method of claim 31, wherein the disease is selected from the group consisting of cardiovascular disease, central nervous system disease and combinations thereof.

20 33. A method according to claim 31, wherein the polymorphic site comprises SEQ ID NO: 3 or 4 or complement thereof.

34. A method according to claim 31, wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1.

35. A method according to claim 31, wherein the polymorphic site is a deletion of 9 25 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2.

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36. A method according to claim 33, wherein the complement of the polymorphic site comprises SEQ ID NO: 5 or 6.
37. A method according to claim 31, wherein the alpha-2B-adrenergic receptor molecule comprises SEQ ID NO. 7 or 8 or fragment thereof.
- 5 38. A method for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule, comprising
  - a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide from the individual; and
  - b. detecting in the sample a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease, thereby diagnosing or prognosing the disease.
39. A method according to claim 38, wherein the disease is a cardiovascular, a central nervous system disease or combinations thereof.
40. A method according to claim 38, wherein the polymorphic site comprises SEQ ID NO: 3 or 4 or complement thereof.
41. A method according to claim 38, wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1.
42. A method according to claim 38, wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2.
43. A method according to claim 40, wherein the complement of the polymorphic site comprises SEQ ID NO: 5 or 6.
44. A method according to claim 38, wherein the alpha-2B adrenergic receptor molecule comprises SEQ ID NO: 7 or 8 or fragment thereof.

45. A method of predicting an individual's response to an agonist or antagonist, comprising:

- obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide from the individual;
- detecting in the sample a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof; and
- correlating the polymorphic site to a predetermined response thereby predicting the individual's response to the agonist or antagonist.

46. A method according to claim 45, wherein the alpha-2B adrenergic receptor molecule comprises SEQ ID NOS. 7 or 8 or fragment thereof.

47. A method according to claim 45, wherein the agonist is an alpha-2B adrenergic receptor agonist.

48. A method according to claim 45, wherein the antagonist is an alpha-2B adrenergic receptor antagonist.

49. A method according to claim 47, wherein the alpha-2B adrenergic receptor agonist is an agonist selected from the group consisting of epinephrine, norepinephrine, clonidine, oxymetazoline, guanabenz, UK14304, BHT933 and combinations thereof.

50. A method according to claim 48, wherein the alpha-2B adrenergic receptor antagonist is an antagonist selected from the group consisting of yohimbine, prazosin, ARC 239, rauwolscine, idazoxan, tolazoline, phentolamine and combinations thereof.

51. A method according to claim 45, wherein the predetermined response to the agonist or antagonist is correlated to adenylyl cyclase, MAP kinase activity, phosphorylation or inositol phosphate levels.

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52. A method according to claim 45, wherein the individual is homozygous for SEQ ID NO: 2 and exhibits a decreased response to the alpha-2B adrenergic receptor agonist.
53. A method according to claim 45, wherein the individual's response is desensitization to the agonist or antagonist.
- 5 54. A method according to claim 47, wherein the individual's response is desensitization to the alpha-2B-adrenergic receptor agonist.
55. A method for selecting an appropriate pharmaceutical composition to administer to an individual having a disease associated with an alpha-2B adrenergic receptor molecule, comprising:
  - a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide from the individual;
  - b. detecting in the sample a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof; and
  - c. selecting the appropriate pharmaceutical composition based on the polymorphic site present.
56. A method of claim 55, wherein the disease is a cardiovascular disease, a central nervous system disease or combinations thereof.
57. A method according to claim 55, wherein the alpha-2B-adrenergic receptor molecule comprises SEQ ID NO. 7 or 8 or fragment thereof.
58. A method according to claim 55, wherein the pharmaceutical composition is an alpha-2B-adrenergic receptor agonist or antagonist.

59. A method according to claim 58, wherein the alpha-2B-adrenergic receptor agonist is an agonist selected from the group consisting of epinephrine, norepinephrine, clonidine, oxymetazoline, guanabenz, UK14304, BHT933, and combinations thereof.

60. A method according to claim 58, wherein the alpha-2B adrenergic receptor antagonist is an antagonist selected from the group consisting of yohimbine, prazosin, ARC 239, rauwolscine, idazoxan, tolazoline, phentolamine and combinations thereof.

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61. A method according to claim 58, wherein the appropriate pharmaceutical composition to administer is correlated to adenylyl cyclase, MAP kinase, phosphorylation or inositol phosphate activity.

10 62. A method according to claim 55, wherein the individual is homozygous for SEQ ID NO: 2 and exhibits a decreased response to the alpha-2B adrenergic receptor agonist.

63. A method of detecting a polymorphic site in a sample to determine alpha-2B-adrenergic receptor function, comprising:

15 a. obtaining the sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement of the polynucleotide; and

b. indirectly detecting in the sample the polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof.

64. A method of detecting a polymorphic site in a sample to determine alpha-2B-adrenergic receptor function, comprising:

20 a. obtaining the sample having an alpha-2B-adrenergic receptor molecule comprising amino acid SEQ ID NO: 7 or 8 or fragment thereof; and

b. indirectly detecting in the sample the polymorphic site at amino acid positions 294 to 309 of SEQ ID NO: 7 or 8.

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